FISH & RICHARDSON P.C.

225 Franklin Street
Boston, Massachusetts
02110-2804

Telephone
617 542-5070

Facsimile
617 542-8906

Web Site
www.fr.com

Date July 3, 2003

To Joyce Tung
U.S. Patent and Trademark Office (Patent)
Commissioner for Patents
Washington, DC 20231
Telephone: (800) 786-9199

Facsimile number 12674-00300001 / ~~1-703-305-3014~~ 703-746-5184

From Y. Rocky Tsao, Ph.D., J.D.

Re DIAGNOSTIC ASSAY OF GENETIC MUTATIONS BY DISCRIMINATING AMPLIFICATION AND HYBRIDIZATION

Applicant:	Harn-Jing Terng, et al
Application No.:	09/915,780
Filing Date:	July 26, 2001
Our Ref.:	12674-003001

Number of pages including this page 5

Message

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225 Franklin Street
Boston, Massachusetts
02110-2804

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617 542-5070

Facsimile
617 542-8906

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VIA FACSIMILE

July 2, 2003

Joyce Tung
U.S. Patent and Trademark Office (Patent)
Commissioner for Patents
Washington, DC 20231

Re: DIAGNOSTIC ASSAY OF GENETIC MUTATIONS BY DISCRIMINATING AMPLIFICATION AND HYBRIDIZATION
Serial NO.: 09/915,780, filed July 26, 2001
Our Ref.: 12674-003001

Dear Examiner Tung:

Thank you for granting a telephone interview, scheduled for 1:00 pm July 3, 2003 to discuss issues raised in the final office action. This letter, limited to claim 1 to facilitate discussion, outlines what we would like to discuss with you during the telephone interview.

Rejection under 35 U.S.C. § 112, first paragraph

Claim 1, rejected for introducing new matter, is drawn to a discrimination primer having a first binding member. In the response filed March 4, 2003, we inserted into the claim the recitation "the first binding member is not labeled directly or indirectly." You contended that this recitation constitutes new matter. To support this position, you pointed out that the primer had a binding member. See the Office Action, page 7, the last paragraph. It seems that you have mistaken "hav[ing] a binding member" for "labeled," and, as a result, erroneously believe that the discrimination primer is labeled.

We would like to point out that "labeled" refers to "linked with a traceable constituent (e.g., enzyme, isotope, and fluorophore)." The specification has disclosed 2 actually prepared discrimination primers, R11-1-3mis18 (SEQ ID NO:2) and RM11-1-3mis18 (SEQ ID NO:3). Neither of them was linked with a traceable constituent, i.e., they were not labeled. See page 8, lines 5-11 of the specification.

In fact, the discrimination primer must be label-free for one to practice the instant invention. To illustrate this point, we attach Exhibit 1. Shown in Exhibit 1A is such a label-free discrimination primer. This primer, together with a labeled amplification primer, allows one to amplify a polymorphism-containing target nucleic acid using the PCR. See Exhibit 1B. After the PCR, one can (1) affix one end of the amplified nucleic acid onto a substrate via the first binding member of the label-free discrimination primer and a second binding member already affixed on a substrate, and (2) detect the bound target nucleic acid via the labeled amplification primer incorporated into the other end of the amplified target nucleic acid. If a discrimination primer were labeled, such as the one shown in Exhibit 1C, one would not be able to detect the bound target nucleic acid since the label d discrimination primer would bind to the substrate and create a high background. Thus, the discrimination primer must be label-free. It follows that the first binding member, an element of the discrimination primer, must also be label-free.

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In other words, the new recitation "the first binding member is not labeled directly or indirectly" merely points out an inherent property of the first binding member and does not introduce any new matter.

Rejection under 35 U.S.C. § 103(a)

You have maintained your rejection against claim 1 as being obvious over Drazen in view of Drmanac. See the Office Action, page 3, lines 5-7. We disagree.

Claim 1 covers a discrimination primer for amplifying a nucleic acid that has a first base at a position suspected of a polymorphism and a second base immediately 3' to the first base. We have illustrated this primer in Exhibit 1A. This primer has (1) a first nucleotide located at the 3' terminus of the primer and contains a base that is complementary to the first base ("S"); (2) a second nucleotide located immediately 5' to the first nucleotide and contains a base that is not complementary to the second base ("X"); (3) a segment of nucleotides located immediately 5' to the second nucleotide and is complementary to a part of the nucleic acid that is immediately 3' to the second base; and (4) a first binding member of a specific binding pair covalently bonded to the 5' terminus of the segment. The first binding member is not labeled directly or indirectly and a second binding member of the binding pair is adapted for affixation on a substrate.

As you have correctly pointed out, Drazen teaches a primer having a mismatch at the penultimate position from its 3' end (Exhibit 2A); Drmanac teaches a method of detecting a target nucleic acid species using a probe that is labeled with a ligand (Exhibit 2B, "Labeled probe"). The ligand serves as a binding member to a traceable constituent such as an enzyme or an antibody labeled with such a traceable constituent. See the Office Action, page 3, line 8 through page 4, line 1. Drmanac also teaches a probe affixed to a substrate (Exhibit 2B, "Affixed probe"). Together, using these two probes allows one to attach a target nucleic acid to a substrate (e.g., Covalink NH) and detect it. See Exhibit 2B.

The combination of Drazen and Drmanac suggests a primer that has a mismatch at the penultimate position and a ligand that is labeled directly or indirectly. See Exhibit 2C. This labeled primer is traceable. To the extent that Drazen and Drmanac suggest a primer having a ligand that is labeled directly or indirectly, and thus traceable, they teach away from the discrimination primer of claim 1, which has a first binding member that is not labeled or traceable. For the reasons set forth above, claim 1 is not obvious over Drazen in view of Drmanac.

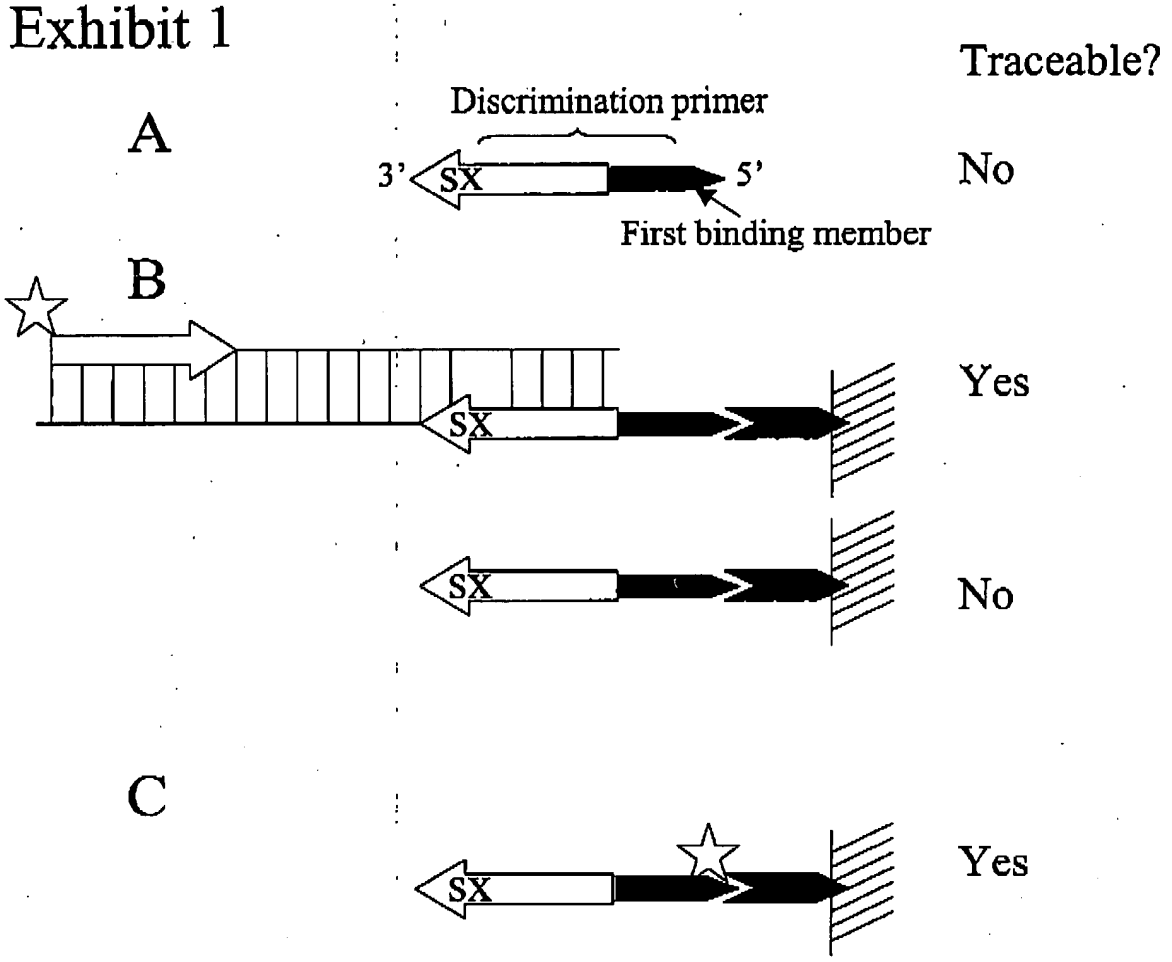
We look forward to discussing with you the above issues at the interview and others on July 3. To expedite the prosecution, we would like to invite your supervisor Gary Benzion to this interview. If you agree, please provide a copy of this letter to him before the interview.

Very truly yours,

Y. Rocky Tsao

Y. Rocky Tsao, Ph.D., J.D.
Reg. No. 34,053

Exhibit 1



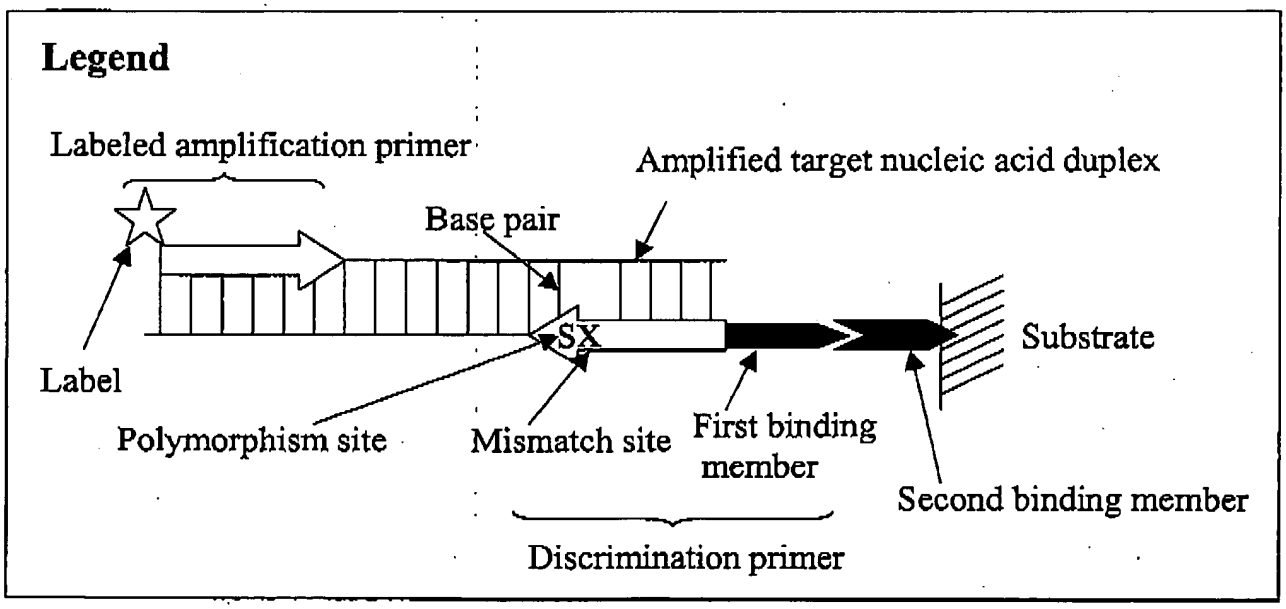
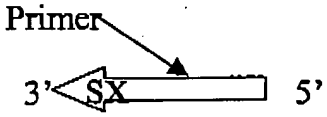
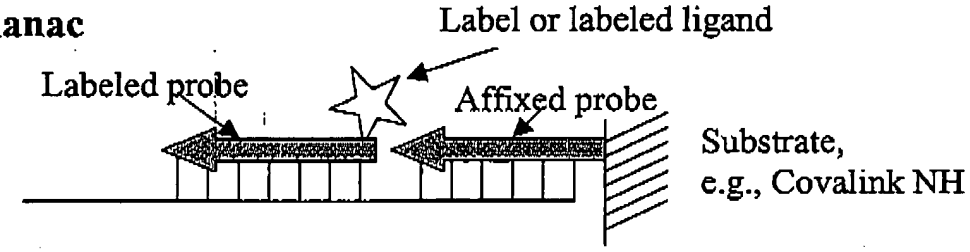


Exhibit 2

A. Drazen



B. Drmanac



C. Drazen + Drmanac